6. (Amended) The plant of claim 3, wherein at least one tissue type of said plant is capable of expressing human acetylcholinesterase, and wherein said human acetylcholinesterase has acetylcholinesterase activity.

13. (Amended) A synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, wherein said synthetic polynucleotide is modified for improved expression in plant cells.

REMARKS

The Office Action of February 27, 2003 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is earnestly requested. Claims 1-15 remain in this case, claims 2, 4-5 and 13, being amended by this response. Claims 8-12 stand withdrawn from consideration, as being directed to non-elected subject matter. The amendment of claims 2 and 4-5 are supported by the original claims. The amendment of claim 13 is supported by the original claims and the specification at page 10, line 23 to page 14, line 5. No new matter has been added.

The Examiner's attention is drawn to the fact that, accompanying this Amendment is Applicant's Petition for Extension of Time and Fee.

Restriction Requirement

Applicant hereby acknowledges the finality of the Restriction Requirement and the Examiner's statement that claims 8-12 are withdrawn from consideration.

In response to Applicant's traversal of the Restriction Requirement, the Examiner states that "Applicant traverses stating that Groups I and II are not distinct." Office Action of February 27, 2003, page 2, paragraph 1, lines 3-4. It is respectfully submitted that the foregoing Examiner's statement is inaccurate: Applicant hereby clarifies that it did not assert that Groups I and II are not distinct. Rather, Applicant's traversal is on the grounds that the Examiner: 1) has not properly applied MPEP 803.04 (Restriction - Nucleotide Sequences), 2) has not properly applied MPEP 803.02 (Restriction - Markush Claims), and 3) has failed to make a proper *prima facie* Restriction Requirement.

Applicant respectfully submits that the Examiner's requirement for restriction has been overcome. Reconsideration of Applicant's grounds for traversal and withdrawal of the finality of the Restriction Requirement are therefore earnestly requested.

Rejection under 35 U.S.C. § 101

Claims 2, 4 and 5 were rejected as claiming unpatentable subject matter under 35 U.S.C. § 101. More particularly, the Examiner maintains that these claims read on wild-type cells, seeds and pollen, since the claimed cells, seeds and pollen were not subjected to a selection step and therefore may not necessarily contain the transgene.

Applicant respectfully disagrees with the rejection. Applicant's claim 1 recites plant cells comprising a polynucleotide that encodes a human acetylcholinesterase. Claim 1 clearly **requires** the claimed subject matter to include a **polynucleotide encoding a human acetylcholinesterase**, such that any composition that does not contain the polynucleotide clearly would fall outside the scope of the claim. Thus, claim 1 cannot encompass wild-type cells, seeds or pollen, as they would not include a polynucleotide encoding a human acetylcholinesterase. Dependent claims 2, 4 and 5, being dependent upon and further limiting independent claim 1, include all of the limitations of claim 1, and thus also cannot encompass wild-type cells, seeds or pollen.

Further, it is respectfully submitted that the specification does, in fact, teach that the transgenic construct includes one or more selectable markers, such as (*e.g.*, NPTII or kanamycin). Specification at page 5, lines 5 and 13, and at Figure 1. Therefore, wild-type cells that do not include the DNA encoding human acetylcholinesterase are <u>not</u> expected to survive the selection process.

On April 16, 2003, Applicant's attorney held a telephone Interview with the Examiner to discuss the rejection, wherein the Examiner maintained the rejection, but stated that the rejection could be overcome by amendment of the claims to expressly recite that the claimed cells include the transgenic construct.

Applicant disagrees with the rejection, however, in the interest of advancing prosecution, claims 2 and 4-5 are hereby amended to recite individually that the claims require a polynucleotide encoding a human acetylcholinesterase. Such amendment does not (and cannot) narrow the scope of the original claims.

It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the rejection of claims 2, 4 and 5 as claiming non-statutory subject matter are therefore respectfully requested.

Rejections under 35 U.S.C. § 112

Claim 6 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More particularly, the Examiner maintains that the meaning of the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) is unclear. Applicant respectfully disagrees with the rejection.

A claim is indefinite only if the scope of the claim would not be clear to one of ordinary skill in the art. It is respectfully submitted that the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) are well known in the art, as exemplified by their extensive use in the prior art. Further, the term "physiologically active" is additionally clarified by Applicant's detailed specification. See, *e.g.*, Fig. 2 (describing activity): "On a per soluble protein basis, high activity, comparable to a third of the activity present in mammalian brain and five times more than that present in muscles, was registered in several of the lines, including AChE-53, AChE-54, AChE-62 and AChE-68. In these lines, activity was on the order of 100 mU/g leaf tissue (fresh weight)." Specification at page 7, lines 21-25; also see generally page 5, line 25 to page 9, line 17.

On April 16, 2003, Applicant's attorney held a telephone Interview with the Examiner to discuss the rejection, wherein the Examiner clarified that the rejection is based on the Examiner's perception that the claim could be construed to require the human acetylcholinesterase to be active in a particular plant tissue. It is respectfully submitted that such construction is repugnant to the plain, ordinary meaning of the claim terms, particularly since human acetylcholinesterase is not expected to have any specific activity within a plant cell per se, based on the teachings of the prior art. Applicant therefore maintains that one of ordinary skill in the art reading the claims would apply the plain, ordinary meaning of the terms "physiologically active" (as applied to a human acetylcholinesterase composition) and "tissue type" (as applied to a plant) and, guided by the specification, would understand the scope of the claim.

Applicant disagrees with the rejection, however, in the interest of advancing prosecution, claim 6 is hereby amended to clarify that at least one tissue type of said plant is capable of expressing human acetylcholinesterase, and said human acetylcholinesterase has acetylcholinesterase activity. Such amendment does not narrow the scope of the original claims, rather, the language of the claim has been rearranged for clarity.

It is respectfully submitted that the rejection has been overcome and that there are no other ambiguities in the claims. Reconsideration and withdrawal of the indefiniteness rejection of claim 6 are therefore respectfully requested.

Claim 14 was rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. More particularly, the Examiner maintains that the specification is merely enabling for expression of human acetylcholinesterase in plant cells, but does not enable expression in non-plant cells (*e.g.*, mammalian, insect, yeast, bacterial). Applicant respectfully disagrees with the rejection.

In making the 112 rejection of claim 14, the Examiner also makes numerous assertions of fact, but cites no authority in support of the factual assertions. If the Examiner's assertions are intended to indicate that the rejection is based on common knowledge in the art or "well known" prior art under MPEP 2144.03, then Applicant traverses the Examiner's assertion.

The test for enablement is whether the disclosure, when originally filed, contained sufficient information regarding the subject matter of the claims as to enable those of ordinary skill in the pertinent art to make and use the invention. The standard is whether the experimentation necessary to practice the invention is undue or unreasonable. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). See also U.S. v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") (emphasis added). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies , Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). The Examiner's analysis must consider all the evidence related to each of the Wands factors, and any conclusion of non-enablement must be based on the evidence as a whole. In re Wands, 858 F.2d at 740, 8 USPQ2d at 1407.

Applicant's claim 14 recites a transformed cell comprising the polynucleotide of claim 13. It should be noted that, although claim 13 requires the polynucleotide to be modified for improved expression in plant cells, neither claim 13 nor 14 requires expression of the polynucleotide in any cell. Thus, claim 14 does not require that the polynucleotide be expressed in a plant cell; all that is required is that the polynucleotide be modified for improved expression in plant cells, and that the polynucleotide be present (*e.g.*, by transformation) in any cell (*i.e.*, either a plant or non-plant cell).

The general rule on adequacy of disclosure is that disclosure of a single species is adequate support for a generic claim. In re Bowen, 181 USPQ 48, 50 (CCPA 1974). It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See* Utter v. Hiraga, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); In re Robins, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). In In re Rasmussen the court restated the uncontroversial proposition that "a claim may be broader than the specific embodiment disclosed in a specification." 211 USPQ 323, 326 (CCPA 1981).

The Examiner admits that Applicant's disclosure enables the expression of human acetylcholinesterase in plant cells. Further, it is respectfully submitted that Applicants are not required to and, in fact, are discouraged from including in their applications that which is already known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The cloning and expression of human acetylcholinesterase in **non-plant cells** is well known in

the prior art. See, *e.g.*, Soreq *et al.* (5,891,725 and 5,595,903), cited by the Examiner in support of the 102 and 103 rejections of the claims. Thus, Applicant's disclosure need not describe cloning and expression of human acetylcholinesterase in **non-plant cells**. Nevertheless, Applicant's disclosure does, in fact, disclose that cloning and expression of human acetylcholinesterase in non-plant cells is known in the art (*e.g.*, by reference to the foregoing patents and corresponding non-patent publications). Applicant further teaches the expression of human acetylcholinesterase in plant cells (in addition to disclosing novel sequences for expression and/or replication in both plant and non-plant cells). Therefore, by reading Applicant's disclosure, combined with the knowledge possessed by one of ordinary skill in the art and the teachings of the prior art, one of ordinary skill in the art would be able to practice the invention of claim 14 without undue experimentation.

Applicant submits herewith its Declaration under 37 C.F.R. § 132, providing additional evidence in support of the foregoing arguments, showing that one of ordinary skill in the art would be able to practice the claimed invention (*i.e.*, expression of human acetylcholinesterase in plant and non-plant cells) without undue experimentation. See attached Declaration of Dr. Tsafrir Mor. It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the enablement rejection of claim 14 are therefore respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 13 and 14 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Soreq *et al.* (U.S. 5,595,903). Claim 13 is amended to overcome the rejection.

Applicant's claim 13, as amended, recites a synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, **wherein said synthetic polynucleotide is modified for improved expression in plant cells**. Soreq (U.S. 5,595,903) does not disclose a synthetic polynucleotide encoding human acetylcholinesterase modified for improved expression in plant cells. Rather, the "synthetic" construct of Soreq is merely a composite of human acetylcholinesterase genomic and cDNA sequences. Therefore, Soreq does not disclose each and every element of Applicant's claim 13. It is respectfully submitted that the rejection is thus overcome. Claim 14, being dependent upon and further limiting claim 13, should be allowable for the same reason, as well as for the additional limitations recited therein. Reconsideration and withdrawal of the rejection of claims 13 and 14 as being anticipated by Soreq are therefore earnestly requested.

Claim 15 was rejected under 35 U.S.C. § 102 (e) as being anticipated by Soreq *et al.* (U.S. 5,891,725). Applicant respectfully disagrees with the rejection.

Claim 15 depends from claim 1, which recites one or more **plant cells** comprising a polynucleotide encoding a human acetylcholinesterase. Soreq (U.S. 5,891,725) does not disclose a **plant cell** comprising a polynucleotide encoding a human acetylcholinesterase. Rather, the reference merely discloses expression in **non-plant cells**. Therefore, Soreq does not disclose each and every element of claim 15. It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the rejection of claim 15 as being anticipated by Soreq are therefore earnestly requested.

Applicant submits herewith its Declaration under 37 C.F.R. § 132, providing additional evidence in support of the foregoing arguments, showing that claims 13-15 are not anticipated by Soreq (5,891,725 and 5,595,903). Reconsideration and withdrawal of the enablement rejection of claims 13, 14 and 15 are respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1-7 and 13-15 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Soreq, as applied to claims 13-15 above, and further in view of Goodman. Applicant respectfully disagrees, and believes the claims, as amended, are patentable over Soreq (both 5,891,725 and 5,595,903) and Goodman, both individually and in combination, for the reasons given above in respect to the section 102 rejections of claims 13-14 and 15. The arguments above as to the novelty of claims 13-14 and 15 are repeated here by reference.

In making the obviousness rejection, the Examiner also asserts that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention, however, the Examiner cites absolutely no authority in support of that factual assertion. If the Examiner's assertion is intended to indicate that the obviousness rejection is based on common knowledge in the art or "well known" prior art under MPEP 2144.03, then Applicant traverses the Examiner's assertion.

It is respectfully submitted that the Examiner has not made a *prima facie* showing of obviousness. More particularly, the Examiner has not shown any evidence in the prior art that suggests one of ordinary skill in the art would have a reasonable expectation of success in expressing active human acetylcholinesterase in plants.

It is well known in the art that expression of foreign genes in plants is highly unpredictable, particularly when the foreign gene is a non-plant gene. For example, Sweetlove *et al.* (1996, Biochem. J. 320:493-498) found no differences in starch content, tuber number, tuber weight, or metabolite content between potatoes transformed with a gene encoding ADP-glucose pyrophosphorylase and potatoes from control plants, even though the activity of the enzyme was four-fold higher in the transformed plants (page 495 and page 497, right column, paragraph 3). Further, Thiele *et al.* (1999, Plant Physiol. 120:73-81) teach that in potato plants transformed with the *Arabidopsis phytochrome* B gene, the endogenous phytochrome B transcript levels were not significantly affected (page 75, right column, paragraph 3, and Fig. 1). Furthermore, genes encoding proteins thought to be directly involved in disease resistance may be ineffective in conferring disease resistance, following their expression in transgenic plants (see, *e.g.*, Linthorst *et al.*, 1989, The Plant Cell 1:285-291, at page 285, Abstract), or may fail to confer protection (see, *e.g.*, Dandekar *et al.*, 1994, Plant Sci. 96:151-162, at page 151, Abstract). Indeed, the prior art as a whole teaches that expression in plants is highly unpredictable. See, *e.g.*, The Plant Cell, vol. 1, 285-291 (1989).

Moreover, at the time of Applicant's invention, it was unknown whether human acetylcholinesterase could be expressed in plant cells at all, let alone whether the protein would have any activity. For example, it was uncertain whether the protein would be co- and/or post-translationally modified (*e.g.*, glycosylation) and/or folded properly when expressed in plant cells. Further, it was unknown, for example, whether the codon frequency of the native human gene would allow it to be expressed in plants in therapeutic amounts. These and numerous other factors made it highly unpredictable whether active human acetylcholinesterase could be produced in plant cells. See attached Declaration of Dr. Tsafrir Mor.

Soreq *et al.* does not address expression of human acetylcholinesterase in plant cells whatsoever, and thus provides absolutely no teaching in this regard. Further, Goodman does not overcome the inherent unpredictability in the art. Indeed, the disclosure and claims of Goodman are strictly limited to the expression of a only a single gene (*i.e.*, interferon) in plants, precisely because that was the only gene Goodman was able to express in plants. Goodman's disclosure clearly is not sufficient to teach expression of any other genes in plants; the art remains unpredictable. The only teaching that active acetylcholinesterase can be expressed in plants comes from Applicant's disclosure. See attached Declaration of Dr. Tsafrir Mor. It is respectfully submitted that the rejection is thus overcome. Reconsideration and withdrawal of the obviousness rejection are therefore earnestly requested.

Applicant submits herewith its Declaration under 37 C.F.R. § 132, providing additional evidence in support of the foregoing arguments, showing that claims 1-7 and 13-15 are non-obvious. Reconsideration and withdrawal of the obviousness rejection of claims 1-7 and 13-15 are respectfully requested.

Applicant believes the claims, as amended, are patentable over the prior art, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, he is invited to telephone the undersigned at the number given below.

"Recognizing that Internet communications are not secured, I hereby authorize the PTO to communicate with me concerning any subject matter of this application by electronic mail. I understand that a copy of these communications will be made of record in the application file."

Respectfully Submitted:

By: Thomas T. Aquilla

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Dated: July 28, 2003

APPENDIX OF AMENDED CLAIMS

The following are the claims in this case, as amended to date, showing all changes made by this response, in compliance with 37 C.F.R. § 1.121(c)(1)(ii):

2. (Amended) A tissue culture of regenerable cells derived from the plant cell of claim 1, wherein said tissue culture comprises one or more cells that include a polynucleotide encoding a human acetylcholinesterase.

4. (Amended) A seed derived from the plant of claim 3, wherein said seed comprises one or more cells that include a polynucleotide encoding a human acetylcholinesterase.

5. (Amended) Pollen derived from the plant of claim 3, wherein said pollen comprises one or more cells that include a polynucleotide encoding a human acetylcholinesterase.

6. (Amended) The plant of claim 3, wherein at least one tissue type of said plant is capable of expressing [a physiologically active] human acetylcholinesterase [in at least one tissue type of said plant], and wherein said human acetylcholinesterase has acetylcholinesterase activity.

13. (Amended) A synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, wherein said synthetic polynucleotide is modified for improved expression in plant cells.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

June 10, 2003

In Re application of: Tsafrir S. Mor *et al.*
Serial No: 09/810,861
Filed: March 16, 2001
For: **EXPRESSION OF RECOMBINANT HUMAN ACETYLCHOLINESTERASE IN TRANSGENIC PLANTS**
Art Unit: 1638
Attorney Docket Number: BTI-45

DECLARATION UNDER 37 CFR § 1.132

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

In response to the Office Action dated February 27, 2003, I, Dr. Tsafrir S. Mor, Ph.D., hereby declare and say as follows:

BACKGROUND INFORMATION

1. I am an Assistant Research Professor in the Arizona Biodesign Institute and the School of Life Sciences at Arizona State University. My ***curriculum vitae***, which describes my education, employment, research publications and other expert qualifications, is **attached hereto as Exhibit 1.**

2. I have extensive experience in the fields of molecular biology and genetic engineering of plants. I have worked in the field of molecular biology since 1988. Through my years of research and professional activities in the fields of molecular biology and genetic engineering of plants, I am familiar with the skills of those working in the field from the early 1980s to the present. In carrying out my current professional activities, I keep up to date on the technical literature and maintain contact with other experts in the field.

3. I am a co-inventor of the invention of claims 1-15 in the present patent application, Ser. No. 09/810,861.

4. I have read and understood the above referenced patent application, including the specification, claims and the relevant prior art, as well as U.S. Patent Nos. 5,891,725 and 5,595,903 to Soreq *et al.*, and U.S. Patent No. 4,956,282 to Goodman *et al.*, cited by the

Examiner in this case in support of the anticipation and obviousness rejections of the claims. Based on my analysis of the contents of the aforementioned documents, I have formulated certain opinions regarding the issues of enablement and the alleged anticipation and obviousness of the claims.

5. The standard I used for anticipation was whether a single prior art reference discloses each and every element or limitation of the claim.

6. The standard I used for obviousness was whether the differences between the subject matter sought to be patented and the prior art are such that the claimed subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art of genetic engineering of plants, and whether the teaching or suggestion is accompanied by an expectation of successfully making the claimed subject matter.

7. The standard I used for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosure in the application coupled with information known in the art, without undue experimentation.

8. A person of ordinary skill in the art would have a Ph.D. in molecular biology or an equivalent degree and at least two years of laboratory research experience in genetic engineering of plants, or at least a B.S. degree and a minimum of four years of laboratory research experience in genetic engineering of plants.

9. Molecular biology, and particularly the genetic engineering of plants, are extremely complex subjects and therefore the art typically engages in complex, time-consuming experimentation. However, the level of skill in the art is high, as attested to by the level of ordinary skill noted above, and the state of the art is relatively advanced, in that complete manuals are available that describe the methods of molecular biology and transformation of plants in great detail.

10. One of ordinary skill in the art would know how to repeat any procedures, published or otherwise known in the prior art, as well as the procedures disclosed in the present patent application, to clone a polynucleotide molecule encoding human acetylcholinesterase, construct appropriate expression vectors and use them for the transformation of many different types of organisms, including plants. Detailed protocols for transformation are available for many types of organisms and their availability is assumed for anyone skilled at the art.

11. Despite this enormous advance in the state of the art as declared above, expressing a particular recombinant protein in plants remains an empiric exercise, which requires custom tailoring and optimization. Unfortunately, except for a few rules of thumb, insights gained while studying one protein cannot be taken for granted when approaching a different expression project and success cannot be guaranteed, or even assumed *a priori*. Nonetheless, by following the disclosed procedures and available prior art, a person skilled at the art, as defined above, would be enabled to obtain the disclosed results.

ENABLEMENT OF CLAIM 14

12. The prior art teaches the cloning and expression of human acetylcholinesterase in non-plant cells. See, *e.g.*, Soreq *et al.*, U.S. Patent Nos. 5,891,725 and 5,595,903.

13. The present patent application, Ser. No. 09/810,861, acknowledges that cloning and expression of human acetylcholinesterase in non-plant cells is known in the art, and further teaches expression of human acetylcholinesterase in plant cells, providing specific examples.

14. Based on the information known in the art combined with the disclosure in the present application, one of ordinary skill in the art could make and use the invention of claim 14, without undue experimentation. More particularly, cloning and expression of human acetylcholinesterase in non-plant cells was known in the art already, and the disclosure of Ser. No. 09/810,861 further enables its expression in plant cells.

NOVELTY OF CLAIMS 13-15

15. The Examiner maintains that Soreq *et al.* (U.S. 5,595,903) anticipates claims 13 and 14. I strongly disagree with the Examiner's conclusion, as explained in further detail below.

16. Amended claims 13 and 14 recite a synthetic polynucleotide comprising a nucleic acid molecule that encodes a human acetylcholinesterase, wherein said synthetic polynucleotide is modified for improved expression in plant cells.

17. Soreq (U.S. 5,595,903) does not disclose a synthetic polynucleotide encoding human acetylcholinesterase modified for improved expression in plant cells. Rather, the "synthetic" construct of Soreq is merely a composite of human acetylcholinesterase genomic and cDNA sequences; it was not modified for improved expression in plants.

18. Therefore, Soreq (U.S. 5,595,903) does not disclose each and every element of claims 13 and 14.

19. The Examiner maintains that Soreq *et al.* (U.S. 5,891,725) anticipates claim 15. I strongly disagree with the Examiner's conclusion, as this clearly is not supported by any evidence and, in fact, it is incorrect, as explained in further detail below.

20. Claim 15 recites one or more plant cells comprising a polynucleotide encoding a human acetylcholinesterase.

21. Soreq (U.S. 5,891,725) does not disclose a plant cell comprising a polynucleotide encoding a human acetylcholinesterase. Rather, the reference merely discloses cloning and expression of human acetylcholinesterase in non-plant cells.

22. Therefore, Soreq (U.S. 5,891,725) does not disclose each and every element of claim 15.

NON-OBVIOUSNESS OF CLAIMS 1-7 and 13-15

23

The Examiner maintains that claims 1-7 and 13-15 are obvious over Soreq, as applied to claims 13-15 above, and further in view of Goodman. I strongly disagree with the Examiner's conclusion of obviousness, and particularly disagree with the Examiner's assertion that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention, as the Examiner's conclusion is not supported by any evidence and, in fact, it is incorrect, as explained in further detail below.

24. Although the state of the art of molecular biology is advanced and the level of skill is high, nevertheless, the expression of foreign genes in plants is highly unpredictable, particularly when the foreign gene is a non-plant gene. Expression of foreign genes in plants, as well as over-expression of plant genes of the same or a different species as the host plant, remains an empirical endeavor, which requires not only skill and patience but ingenuity, inspiration and inventiveness.

25. At the time of the present invention, it was unknown whether human acetylcholinesterase could be expressed in plant cells at all, let alone whether the protein would have any activity. For example, it was uncertain whether the protein would be co- and/or post-translationally modified (*e.g.*, glycosylation) and/or folded properly when expressed in plant cells. Further, it was unknown, for example, whether the codon frequency of the native human gene would allow it to be expressed in plants in therapeutic amounts. These and numerous other factors made it highly unpredictable whether active human acetylcholinesterase could be produced in

plant cells. These include features of the mRNA including the very high G/C content of the gene and transcript making it prone to forming very tight secondary structures, which may limit its translatability (among other factors). Thus getting the human gene to express at all, prior to its optimization for expression in plant cells, was actually quite surprising.

26. Soreq *et al.* does not address expression of human acetylcholinesterase in plant cells whatsoever, and thus provides absolutely no teaching in this regard.

27. The disclosure and claims of Goodman are strictly limited to the expression of interferon in plants, precisely because that was the only gene Goodman was able to express in plants. Goodman's disclosure clearly is not sufficient to teach expression of any other genes in plants; this is merely one example and the art remains highly unpredictable.

28. As far as I am aware, the present application provides the only teaching that active acetylcholinesterase can be expressed in plants.

CONCLUSION

29. Based on the above analysis, I conclude that the claims in the present patent application are enabled and both novel and non-obvious over the prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: July 18th 2003 By: _____
Dr. Tsafrir S. Mor, Ph.D.

Tsafrir S. Mor

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EDUCATION

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Hebrew University of Jerusalem, Jerusalem, Israel	B.Sc.	1989 (*cum laude*)	Biology
Hebrew University of Jerusalem, Jerusalem, Israel	M.Sc.	1995	Biochemistry
Hebrew University of Jerusalem, Jerusalem, Israel	Ph.D.	1997	Biochemistry

PROFESSIONAL EXPERIENCE:

1982-1985	Military service
1989-1996	Teaching Assistant, The Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel.
1, 1992	Visiting scientist with Dr. Susan S. Golden (Texas A&M University, College Station, TX, USA)
8/92-1/1993	Visiting scientist with Dr. Himadri B. Pakrasi (Washington University, St. Louis, MO, USA)
8-9/1993	Visiting scientist with Dr. Himadri B. Pakrasi (Washington University, St. Louis, MO, USA)
9, 1995	Visiting scientist with Dr. Jean-David Rochaix (University of Geneva, Geneva, Switzerland)
12/1996-4/1997	Post-Doctoral Fellow, The Department of Biological Chemistry, The Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
1997-2000	Post-Doctoral Associate, Boyce Thompson Institute for Plant Research at Cornell University, Tower Rd., Ithaca, NY 14853, USA
2000-2003	Research Assistant Professor, Dept. of Plant Biology, Arizona State University, Tempe, AZ 85287
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HONORS AND AWARDS:

1987	Dean's Prize, Hebrew University of Jerusalem
1988	Dean's List, Hebrew University of Jerusalem
1990	Edith Polak Prize, Hebrew University of Jerusalem
1991	Rector's Prize, Hebrew University of Jerusalem
1997	Fullbright Post-doctoral fellowship (declined)
1997-1999	2-year Postdoctoral Award (No. FI-251-97) from the US-Israel Binational Agricultural Research and Development Fund
1999	1 year competitive grant awarded by the Boyce Thompson Institute

2001	Principal Investigator on a 3 year contract with Defense Advanced Research Project Agency, US Department of Defense (#N66001-01-C-8015) to develop countermeasures against chemical and biological threats. Total contract value $1,555,035.

ORAL PRESENTATIONS IN INTERNATIONAL FORUMS:

Mor, T. S., Richter, L. and Mason, H. S. (1998). Expression of Rotavirus proteins in transgenic plants. In *The IX International Congress on Plant Tissue and Cell Culture.* Jerusalem, Israel. June 14-19, 1998. Abstract 0183.

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Thesis

Mor, T. S. (1996) *Dynamics of Photosystem II: Structural and Functional Aspects of Proteins Associated with the Reaction Center.* Academon Press, Jerusalem.

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Gal, A., **Mor, T. S.**, Hauska, G., Herrmann, R. and I. Ohad, I. (1990). LHCII kinase activity associated with Isolated Cytochrome b6/f complex. In Current Research in Photosynthesis. (Baltscheffski, M., ed.). vol. I, pp. 783-785. Kluver Academic Press, Dordrecht.

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Mason, H. S., Palmer, K. E., Hefferon, K. L., Mor, T. S., and Arntzen, C. J. (2002). Geminivirus Vectors for Gene Expression in Plants. In USPTO (US 6,392,121 B1, Boyce Thompson Institute for Plant Research, Ithaca, NY (US))

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